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Review Article

A Review on Different Solubility Enhancement Techniques of Ticagrelor

Abhishek Srivastava[1,*], Mohammad Ahmad Khan[2], Simrata Bedi[1], Uma Bhandari[2]

[1]Formulation Research and Development-Orals, Sun Pharmaceutical Industries Ltd., Gurugram, Haryana, INDIA.
[2]Department of Pharmacology, School of Pharmaceutical Education and Research Jamia Hamdard, New Delhi, INDIA.

ABSTRACT

Ticagrelor is a BCS class IV drug that inhibits platelet action by reversibly binding to the P2Y12 receptor. One of the major challenges faced by the class IV (low solubility, low permeability) drug is the lower dissolution rate leading to low bioavailability. The bioavailability of the marketed formulation of ticagrelor is approximately 36%. Researchers have come up with various techniques to improve the BCS class II and IV drug formulations as an integral part of the development of the pharmaceutical sciences. An increase in solubility can be achieved by various methods such as Salt formation, Complexation, Micronization, Solid Dispersion, altering the pH, Co-solvency, co-crystals, polymeric micelles, etc. A highly efficacious technique is converting a crystalline drug to its amorphous form. An extensive literature search was conducted using various databases like science direct, Taylor and Francis, Springer to extract relevant articles. Keywords like "Ticagrelor", "low permeability", "P2Y12 receptor inhibitor" were used for the literature search. Relevant articles were screened and referred for further study. This article discusses the techniques employed to increase the solubility of ticagrelor, thus highlighting the research conducted and reported. The increase in bioavailability of ticagrelor could be seen when formulated as nanoparticles, co-crystals, ticagrelor loaded self-micro emulsifying and nano emulsifying drug delivery system, solid dispersion, etc. the conversion of the crystalline drug into amorphous drug is a highly recommended approach to increase the solubility of ticagrelor which can be seen in cases of co-crystals and solid dispersion formulation.

Keywords: Ticagrelor, Bioavailability, Antiplatelet drug, Solubility enhancement, P2Y12 receptor, BCS classification.

Correspondence
Mr. Abhishek Srivastava
Formulation Research and Development-Orals, Sun Pharmaceutical Industries Ltd., Gurugram-122015, Haryana, INDIA.
Email id: abhishek.sri@sunpharma.com

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INTRODUCTION

Drug delivery by the oral route is the simplest route of administration and consists of the majority of the formulations available in the market. It has the advantage of dose precision, small bulk size, and ease of manufacturing. The majority of the drugs and new chemical entities adopt solid dosage form techniques, such as powders, tablets, capsules, etc.[1] A Biopharmaceutics classification system has been designed which divides the molecules on basis of solubility and permeability into four classes.[2] Class II and Class IV have low solubility and are highly inclined to research by professionals. The continuous challenge to develop a more efficacious formulation for both classes are of major concern. One of the prime targets to do so is the enhancement of solubility of these drugs.[3]

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SOLUBILITY

Solubility is characterized as the sum of substance that passes into the solution to form a saturated solution at steady temperature and pressure. Solubility can be framed in terms of the maximum volume or mass of the solute that breaks up in a given volume or mass of a solvent.[2] An increase in solubility can be achieved by various methods such as Salt formation, Complexation, Micronization,[4] Solid Dispersion, altering the pH, co-solvency, co-crystals, polymeric micelles, etc.[5] A highly efficacious technique is the conversion of a crystalline drug to its amorphous form. Amorphous drugs have better solubility than crystalline drugs due to their structure, increased surface area, and better wettability.[6] The amorphous state has better solubility as it has higher entropy, enthalpy, volume, and free energy when compared to its crystalline structure.[7]

TICAGRELOR

Ticagrelor is classified as an anti-platelet aggregator, which reversibly binds to the P2Y12 receptor and acts by antagonizing the binding of adenosine phosphate to the P2Y12 receptor resulting in decreased uptake of adenosine. It is a direct-acting and immediate-release drug taken orally. Both the active drug

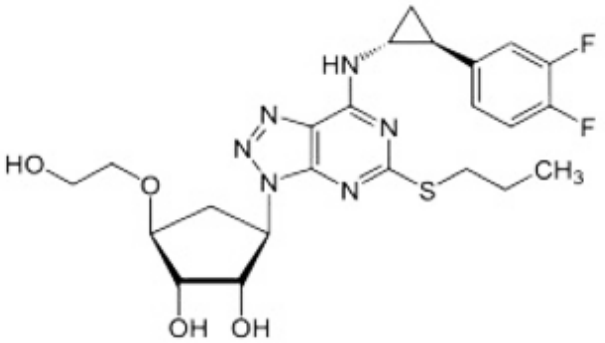

Figure 1: Structure of Ticagrelor.

and its metabolite have approximately equal potencies. Figure 1 represents the structure of the Ticagrelor.

Ticagrelor is administered along with aspirin in cases of strokes, myocardial infarctions, and other acute coronary syndromes.[1] It is a tasteless drug being poorly soluble. The drug also has a reported bioavailability of 36%. Ticagrelor is a BCS class IV drug having low Solubility and low permeability. Ticagrelor is one of the modest drugs prescribed in cases of Acute Coronary Syndrome, owing to its irreversible binding to the $P2Y_{12}$ receptor.[8] AstraZeneca got the approval for ticagrelor in 2011 by the FDA.[9] Ticagrelor has a loading dose of 180 mg followed by 90 mg twice daily.[10] It has a rapid onset and offset of effects due to its direct and reversible mode of action.[11] Ticagrelor belongs to the class known as cyclopentyl triazolopyrimidines and the chemical name of the compound is (1S,2S,3R,5S)-3-[7-[[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-1,2-cyclopentanediol.[9] The metabolism of the drug takes place with the help of CYP3A and the renal clearance of the drug is negligible. Ticagrelor is a substrate of P-gP and weakly inhibits the activity of P-gp.[12] The present antithrombotic therapy is decided based on the risk of occurrence of any thrombotic event, bleeding, and presence of the disease. The therapy includes the risk of occurrence of bleeding in ACS patients. Ticagrelor decreases the risk of occurrence of such events, thereby eliminating the inter-variability of the effect in patients. Continuous development in antithrombotic therapy is being made for a safer and improved therapy.[13,14] The solubility of ticagrelor, analyzed using HPLC in some of the solvents in the decreasing order is as follows: cyclohexanone > 2-butanone > methanol > ethyl acetate > ethanol > 1-butanol > propanol > isopropanol > n-octanol > isobutanol > acetonitrile > toluene.[15] This is one of the major challenges for formulators to increase the bioavailability of the anti-platelet drug. Ticagrelor is rapidly absorbed having t_{max} of 1.3-2.0 hr. after single dosage administration and t_{max} is delayed to 1.5-3.0 hr. in case of multiple dosage regimen. Ticagrelor and its metabolite are majorly metabolized by the liver and pass into bile for excretion through the intestine via intestinal P-glycoprotein. Ticagrelor is a substrate and inhibitor of P-gP.[16] PLATO (Platelet Inhibition and Patient Outcomes) Study: A study on 18,624 patients with ACS concluded that the risk of stroke, myocardial infarction, and death related to vascular causes was reduced in patients with ticagrelor administration compared to clopidogrel (9.8% vs 11.7% respectively), without any signs of an increase in bleeding.[17,18] The major difference between ticagrelor and its other thienopyridine counterparts is that the former does not exist as a prodrug. There is no requirement for biotransformation or any king of enzymatic metabolism. Also, the reversible binding property of ticagrelor makes it a novel antiplatelet therapy. The PLATO trial compared the molecule with other anti-platelet molecules and demonstrated an improved clinical response to clopidogrel. It also showed uniform and superior platelet inhibition, which was associated with a low prevalence of high on-treatment platelet activity.[19]

Recent advancements for solubility enhancement of ticagrelor

A study was conducted to examine the relative bioavailability of Ticagrelor pediatric tablets and granules for oral suspension to the adult immediate-release table available in the market as the commercial formulation. The C_{max} and AUC both completely lied between the confidence interval of 80.00-125.00% for the drug and is an active metabolite. The drug plasma concentration-time profile for the drug and its metabolite were similar for all the formulations. Ticagrelor showed rapid absorption with t_{max} ranging from 2-2.5 hr. and its metabolite, AR-C124910XX having t_{max} of 2.5-3.0 hr. The mean terminal elimination half-life of the drug and its metabolite is 8.2-8.3 hr and 8.7-9.1 hr respectively.[1] Many formulations have been developed using similar excipients to that of the reference products to create a mirrored *in-vitro* dissolution profile. The developed formulation was evaluated for powder flow characteristics such as tapped density, bulk density, Hausner's ratio, compressibility index, and angle of repose. The tablets were evaluated for in-process quality tests such as friability, hardness, weight variation, disintegration, dissolution, and content uniformity. The tablet was prepared by using the wet granulation method as well as by direct compression method. The dissolution profile was seen at its peak (96.6 ± 0.25) in the Ticagrelor formulation incorporating Hypromellose (HPMC-2910, 5cps) as a granulating agent. Formulation consisted of: Ticagrelor (34.61%), mannitol (61.15%), sodium starch glycolate (2.69%), Hypromellose (HPMC-2910, 5cps) (0.77%), purified talc (0.38%), magnesium stearate (0.38%) and Opadry grey (21k57558) (2%).[20]

Ticagrelor nanoparticles were prepared using solvent-antisolvent technology to increase the solubility and dissolution rate of the poorly soluble drug.[21] The drug was formulated with poloxamer 188 (PXM), polyvinyl pyrrolidine (PVPK-30), and hydroxypropyl methylcellulose (HPMC) as stabilizing agents in different concentrations such as 1:0.5, 1:1, 1:2. The rationale of the

experiment was to decrease the particle size to nano-range which in turn increases surface area to increase the dissolution rate. The drug dissolved in methanol was injected into the stabilizing agent solution using an infusion pump. The precipitated solid particles were freeze-dried to obtain a nanoparticulate powder of the formulation.[22] The formulation with hydroxypropyl methylcellulose (Drug: HPMC-1:1) as stabilizing agent showed good results. The solubility of the formulation increased up to nine times compared to the pure drug. The dissolution efficiency of the optimum formulation was 92% and 88% in pH 1.2 HCl buffer and pH 6.8 phosphate buffer respectively while that of the marketed formulation was 89% and 85%, the similarity factor(f2) being 75 and 70 respectively. This nanoprecipitation method works on the nanosizing of particles responsible for enhanced solubility.[3] Ticagrelor is formulated with PVP-K25 (Povidone) in different ratios (povidone: drug- 0.2:1-1.67:1) using the co-grinding technique. The formulations with a high ratio of povidones showed good disintegration and dissolution rates. The dissolution rate of the best-optimized formulation was more than 92% after 30 min while that of standard ticagrelor was only 22% after 30 min. The dissolution enhancement may be due to the formation of a ticagrelor-PVP K25 soluble complex. The drug release of different formulations with ratios of PVP K25 and ticagrelor ranging from 0.8:1 to 1.67:1 was found to be 81%, 92.1%, 93.5%, 92%, and 93.2%, respectively, after 30 min. The formulations were found to be stable when kept at 40°C/75% RH for 6 months. The optimization batches 1:1 and 1.33 showed dissolution of more than 92%. The solubility enhancement may be a result of the formation of a Ticagrelor-PVP K25 soluble complex.[5] Ticagrelor SNEDDS was formulated as a novel formulation to enhance solubility and dissolution rate. Ticagrelor was formulated into SNEDDS using surfactants polyoxyethylene sorbitan monooleate (Tween 80) and medium-chain triglyceride (MCT) oil, while Labrafil M1944CS was used as co-surfactant. The liquid formulation with the ratio of 20:70:10 (oil: surfactant: cosurfactant) was found to give optimum results with the smallest emulsion droplet size being around 20.56±0.70 nm. The liquid formulation was later converted into powder by spray drying using suitable inert carriers. The solid SNEDDS prepared using Silicon dioxide as a carrier showed a significant increase in the dissolution rate to pure ticagrelor.[23] The development of co-crystals of ticagrelor with aspirin to make a synergistically active molecule was first carried out in the year 2016.[24] The co-crystal was prepared by the solution crystallization technique of ticagrelor and nicotinamide in the ratio of 1:1 formulated along with a co-former. The formation of co-crystals was confirmed by their characterization using FTIR, XRD, and DSC studies. The ticagrelor-nicotinamide co-crystals and ticagrelor-nicotinamide hydrate co-crystals were prepared using ethyl acetate as solvent. Both of them showed an increase of four and four and a half times increase in solubility (in pH 2 acidic medium) respectively and a better *in-vitro* dissolution profile than the commercial product. Also, the ticagrelor-nicotinamide hydrate co-crystals showed a faster dissolution rate than the ticagrelor-nicotinamide co-crystals despite having the same t_{max}.[25] Another one of the ticagrelor SNEDDS was formulated using Miglyol 810, Brij 35, and Lauro glycol FCC as oil, surfactant, and co-surfactant on basis of the solubility of ticagrelor in these components. The formulations were evaluated for drug content, % transmittance, and *in vitro* drug release. The optimum formulation showed a drug release of 98.99% in 60 minutes and that of pure ticagrelor was found to be 31.99%. Evaluation parameters of the optimized formulation such as zeta potential, particle size, and Z average were found to be 18.3 mV, 289.6 nm, and 185.1 nm respectively. The stability of the formulation is confirmed using FTIR and SEM studies. The *in vivo* study of the optimized formulation on Wistar rats indicates a 5-fold increase in oral bioavailability of the formulation when compared to pure ticagrelor. The C_{max} of the optimized ticagrelor SNEDDS was 302.43±4.78 ng/ml which was higher than that of pure ticagrelor suspension 47.32±2.75 ng/ml. Ticagrelor-loaded self-nano emulsifying drug delivery shows a significant improvement in solubility and oral bioavailability of the drug.[26]

A novel pH-sensitive nanocomposite hydrogel was formulated using thiolated chitosan-based nanoparticles of Ticagrelor to increase the oral bioavailability of the drug. The novel pH-sensitive nanocomposite hydrogel was prepared using the radical polymerization technique using different concentrations of acrylic acid as a monomer, chitosan as biodegradable polymer, N, N-methylene bisacrylamide as cross-linker, and potassium persulphate as initiator. The optimized chitosan-based nanoparticles were prepared based on drug loading, swelling studies, gel fraction, and *in vitro* drug release. The *in vitro* release profile and extent of hydrogel swelling were comparatively higher in pH 7.2 phosphate buffer. The bioavailability of the optimized formulation was increased as indicated by prolonged half-life and a multi-fold increase in area under the curve (AUC) when compared to the pure drug. The nanocomposite hydrogels had a pH-responsive controlled behavior and had an increase in the bioavailability of the drug delivered through the oral route.[27] Ticagrelor solid dispersion prepared using TPGS and Neusilin US2 using the solvent evaporation methods improved the drug release.

Solid dispersion can be defined as the dispersion of a hydrophobic drug molecule in a hydrophilic carrier.[7] Solid dispersion classification based on carriers: First-generation SD (crystalline carrier), second-generation SD (amorphous carrier), third-generation (surfactant polymer), and fourth-generation (release modifiers).[28] The technology has been highly researched but the market availability of solid dispersion is low indicating the low advancement of technology.[29] Characterization of the solid dispersion is mainly done by Differential Scanning Calorimetry and X-ray Diffraction.[30] Solid dispersion can be formulated using

various techniques such as hot-melt extrusion,[31] spray drying method,[32] slow solvent evaporation,[33] fusion method,[34] melt agglomeration method, melting (fusion),[35] solvent evaporation,[36] melting-solvent method[28] etc. Hot Melt Extrusion is an efficient solvent-free technology widely being used in the pharmaceutical industry.[37] The ration of ticagrelor: TPGS: Neusilin US2 was kept 1:2:2 w/w/w and was dissolved in ethanol which was later evaporated to obtain the dispersion. The increase in drug release can be attributed to the conversion of the crystalline drug into amorphous, which was confirmed by SEM, DSC, and XRD. The drug release of the dispersion after 90 minutes increased by 34-folds when compared to the ticagrelor commercial product (Brilinta®) and 2.2-folds when compared to the physical mixture of the solid dispersion. The drug release of ticagrelor solid dispersion in pH 1.2, pH 6.8, and distilled water at 90 min was 79.3 ± 0.7%, 76.0 ± 1.4%, and 79.4 ± 3.8%. The permeability of the drug improved by 1.4 times and the efflux ratio decreased by 0.45 times. The C_{max} and relative bioavailability solid dispersion were found to be 238.09 ± 25.96% and 219.78 ± 36.33% respectively.[8] The patent for ticagrelor solid dispersion can be found where the drug is dispersed in the polymers (HPMC, PVP, and soluplus) using the solvent evaporation technique and hot melt method. The dispersion formed with Hydroxypropyl methylcellulose showed the best results among all three polymers.[29] SMEDDS of TCG is formulated to increase the solubility and dissolution of the drug. The formulation consists of 10.0% Capmul MCM (oil), 36.2% Transcutol P (cosurfactant), and 53.8% Cremophor EL (surfactant). The dissolution profile of the SMEDDS formulation in pH 1.2, pH 4.0, pH 6.8 media, and distilled water was found to be more than 85% in 30 minutes, the drug release percentage being 89.4%, 90.8%, 86.5%, and 97.11% respectively. The TCG-SMEDDS showed an increase in permeability to pure Ticagrelor in Caco-2 cells. also, TCG-SMEDDS show higher bioavailability, AUC and C_{max} being 5.7 and 6.4 times higher than that of raw TCG-suspension. The antiplatelet effect of the drug in SMEDDS showed significant improvement as the raw TCG suspension with a dose of 10 mg/kg and TCG-SMEDDS with a dose of 5 mg/kg showed a similar area under the inhibitory curve (907.0%±408.8% and 907.8%±200.5%·hours, respectively).[38]

Co-crystals of ticagrelor with L-tartaric acid were formed by the formation of H-bonds between them which increases the solubility of the pure drug. The co-crystals were prepared with the drug: L-tartaric acid in the ratio 1:1, 2:1, and 1:2 using the solvent evaporation method. The co-crystals of the ratio 1:1 and 2:1 formed stable formulations confirmed by XRD, DCS, and FTIR. The increase in solubility of both the formulations was found to be about 2.7 and 2.6 times when compared to pure API. After 24 hr, the saturation solubility of pure ticagrelor in USP pH 3.0 was found to be 2.5µg/mL.[39]

Ticagrelor-loaded Nanostructured lipid carriers were prepared using the hot melt emulsification ultra-sonification and freeze-dried using the lyophilization technique. The optimization batch formulation had a particle size of 87.6 nm with a capsulation efficiency of 92.1%. The Caco-2 cell permeability study showed that the ticagrelor-loaded nanostructured lipid carrier had a permeability 1.56 times higher than that of raw ticagrelor. The oral bioavailability of the formulation was 254.99% times higher than that of the raw ticagrelor, showing superiority in the antiplatelet action.[40]

Orodispersible tablets are buccal drug delivery systems aimed to release the drug in the buccal cavity and dare not be meant to be swallowed. Ticagrelor orodispersible tablets were assessed for their platelet reactivity and compared with standard ticagrelor. The platelet reactivity was measured by platelet reactivity units. The ticagrelor orodispersible tablets and standard tablets were given to STEMI or very high-risk NSTEMI randomly and the platelet activity was assessed after 1, 2, 4 and 6 hours after the administration of a loading dose of 180 mg. The platelet reactivity units after an hour of administration of loading dose were 97±99 and 115±92 which was numerically lower. The percent platelet inhibition of the ticagrelor orodispersible tablets and the ticagrelor standard tablets was found to be 55±44% and 42±44% respectively.[41]

Ticagrelor nanosuspension is often formulated to overcome the low solubility of the drug. TCG-nanosuspension was formulated using D- α-Tocopherol polyethylene glycol 1000 succinate (TPGS) and polyvinyl alcohol (PVA) which had a particle size (drug) of 233 nm and showed precipitation of 3%. The evaluation of nanosuspension shows conversion of crystalline form to the amorphous form of the drug and also a supersaturation effect, leading to the higher dissolution of the formulation. Pharmacokinetic and gut-sac studies show that TCG-nanosuspension improved the gastro-intestinal permeability by 2.8-fold thereby, increasing the bioavailability by 2.2-folds, compared to the commercial production of ticagrelor. Nanosuspensions could be an effective way to increase the dissolution and bioavailability of a poorly soluble drug.[42] Solid Dispersion adsorbates of ticagrelor prepared by melt adsorption technique and followed by an amalgamation of the dispersion. Some of the advantages of using the melt adsorption technique are the simplicity of the method, ease of scale-up, and economic and solvent-free process. The DSC, XRD, and SEM show the conversion of crystalline drugs to amorphous drugs. The drug release of solid dispersion adsorbates was found to be 86.47% while that of conventional tablets was 6.59%. The formulation also showed an increase of 3.83-folds in permeability during the study of the Caco-2 cell. The relative bioavailability of TCG-solid dispersion adsorbates was found to be 748.53% and 153.43% as compared to TCG-suspension and TCG-conventional tablets respectively in rats. The increased antiplatelet effect can be due to an increase in wettability of the drug, inhibition of P-gp efflux by PEG-4000, or a decrease in the crystallinity of the drug.[43] The

use of ß-cyclodextrin as a carrier in the delivery of ticagrelor has proven to show a drug release of 96.62% within an hour showing the immediate release profile of the drug. Thiol modification of ß-cyclodextrin can also be used as a carrier and is proven safe after *in-vivo* analysis.[44]

The development of a nanosuspension of ticagrelor was done to overcome adverse effects caused by cosolvent mixtures. The nanosuspension was formulated using the wet-milling method and the particle size of the suspension was found to be around 230 nm. Stability studies were carried out at room temperature and refrigerated conditions and the formulation was stable for up to 10 months. The pharmacokinetics and hemodynamic study done on two dog models and one rat model shows dose-independent effects. The developed ticagrelor nanosuspension meant for IV administration was stable.[45] One of the major drawbacks of antiplatelet therapy not found in ticagrelor is its rapid onset of action rather than a suboptimal speed for the onset of action. Also, ticagrelor shows low variability in pharmacological response compared to other anti-platelet drugs.[46]

Solidification of the ticagrelor-loaded self-micro emulsifying drug delivery system is done to increase the dissolution and bioavailability of the drug. The poorly water-soluble drug is dissolved in a self-micro emulsifying drug delivery system which was later adsorbed on an optimized adsorbent for the solidification process. The adsorbent was optimized via a suitable statistical design on basis of their physical properties (tapped density, bulk density, angle of repose, and capacity of liquid adsorption). Neusilin US2 (silica-based adsorbent) and Florite R (non-silica-based adsorbent) were used in the experiment and the mixture ratio was optimized using a statistical experimental design. The solidified ticagrelor self-micro emulsifying drug delivery system was mixed with a binder-PVP, disintegrant-croscarmellose sodium, diluent-MCC, and lubricant-Mg Sterate, granulated, and used to formulate an oval-shaped tablet. The prepared tablet maintained its self-micro emulsifying ability and showed enhanced dissolution of ticagrelor. The *in-vivo* pharmacokinetic study of the formulation shows a relative bioavailability of 108.1% and 632.7% when compares to ticagrelor self-micro emulsifying drug delivery system and pure ticagrelor. A new approach to solidification of SMEDDS was seen and successfully increased the bioavailability of the drug.[47]

Spray drying based on the solvent evaporation method is used to prepare a dispersion of ticagrelor in a hydrophilic polymer matrix. The ticagrelor solid dispersion was evaluated for DSC, FTIR, *in-vitro* dissolution, permeation study, and *in-vivo* bioavailability study. The DSC study shows the presence of the drug in amorphous form and FTIR shows that the polymer and drug are compatible. The drug release profile shows a release of more than 75% after 45 minutes. The *in-vivo* bioavailability studies carried out suggest a more than two-fold increase in bioavailability when compared to the marketed formulation of ticagrelor. The spray drying process used for the preparation of solid dispersion is an effective method to increase the solubility of poorly water-soluble drugs. Experiments also show that a multifunctional drug carrier made up of cyanocobalamin and chitosan could improve the solubility of ticagrelor. The drug-loaded carrier has high drug loading efficiency, appropriate surface charge, low toxicity, suitable particle size and shows a controlled release drug profile. The drug-loaded carrier was evaluated for *in-vitro* drug release, drug loading, and *in-vitro* cytotoxicity.[48,49] The drug-loaded carrier showed a controlled release profile in 0.2% w/v polysorbate-80 in water along with a maximum of 80% drug loading. The cytotoxicity studies of the formulation showed similar results as of the free drug. The proposed drug delivery system could overcome the issues related to the low solubility of the drug and be safe to use.[50,51]

CONCLUSION

The advancement in techniques and technology has led the research in a great place with abundant opportunities. Pharmaceutical science has developed many formulations to develop new formulations and to increase the efficacy of the existing formulations. The developed formulations have seen a drastic increase in solubility of ticagrelor resulting in a higher dissolution rate. The increase in bioavailability of ticagrelor could be seen when formulated as nanoparticles, co-crystals, ticagrelor loaded self-micro emulsifying and nano emulsifying drug delivery system, solid dispersion, etc. the conversion of the crystalline drug into amorphous drug is a highly recommended approach to increase the solubility of ticagrelor which can be seen in cases of co-crystals and solid dispersion formulation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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